REVIEW

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A Systematic Review And Meta-Analysis Comparing The Prognoses Of Benign Thyroid Nodules Using Radiofrequency Ablation Versus Lobectomy

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Abstract

Background: The evolution of technology and medicine has allowed for a considerable number of alternatives for treating medical issues, particularly those requiring invasive surgery. Thyroid nodules consisting of abnormal benign tissue are conventionally managed with surgery (lobectomy); however, advancements have introduced radiofrequency ablation as a method to manage these nodules. The two interventions have shown similar efficacies and no conclusive determination has been reported that proves which method (if any) has the lower recurrence rate. Therefore, this systematic review and meta-analysis was designed to fill this information gap. **Materials and Methods:** Articles were selected based on eligible criteria and the PRISMA algorithm using the electronic databases PubMed, Science Direct, and Europe PMC and the PICO terms "radiofrequency ablation", "lobectomy", "benign thyroid nodule", and "recurrences". Eligible studies were subsequently assessed using the risk bias criteria of the Quality Appraisal of Case Series Studies Checklist and processed with the BUGSnet package in R studio. The results were presented in Funnel and Forest plots. **Results:** Of the 18 eligible studies, 14 involved radiofrequency ablation and 5 involved lobectomies. The recurrence rate using the lobectomy procedure was 11 % (95 % CI, 2–40 %), whereas that with radiofrequency ablation was 4 % (95 % CI, 2–10 %)(p-value < 0.05). Both intervention populations showed high heterogeneity (I2>60 %). **Conclusions:** The recurrence rate of radiofrequency ablation was lower compared to that of lobectomy; however, the high heterogeneity, low sample numbers, lack of direct comparison, and homogeneous design of the studies suggest that further testing is required to confirm this finding.

Keywords: Thyroid nodule- Lobectomy- Prognosis- Radiofrequency ablation- Recurrence

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Introduction

Thyroid nodules are generally benign and do not require therapy. However, management of these nodules is performed in certain cases for symptom relief and cosmetic purposes. According to the American Thyroid Association, thyroid nodules are restricted small abnormal growths that can progress into neoplasms or non-neoplasmic tissue [1]. Other studies have described thyroid nodules as benign thyroid adenomas that are formed from gland structures directly. This definition is more specific than the term nodule and encompasses cysts, carcinomas, lobules that originate from normal tissue, and other focal lesions that differ from normal tissue [1, 2].

The quadruple test approach involves a thorough physical examination, thyroid ultrasonography (USG), TSH serum examination, and fine needle aspiration biopsy (FNAB) is considered the most effective method to determine the appropriate treatment for thyroid nodules [3]. The available treatments are surgery, radio intervention, and hormone intervention. Depending on the affected area of the thyroid gland, a lobectomy can be partial (at the isthmus), subtotal, or total. Radioactive iodine ablation involves the use of devices to generate an alternating electric field within the target lesion using a needle electrode connected to an external radiofrequency generator. The rapid movement of ions is followed by progressive heating of the tissue and eventual thermal necrosis [4]. The radiofrequency ablation procedure can be performed under local anesthesia or conscious sedation. A cervical trans-isthmic approach is used to place the electrodes in the distal part of the nodule, and after ablation of the initial zone, the electrodes are systematically inserted into the central and more proximal areas of the thyroid lesion. This radiofrequency technique results in multiple confluent areas of thermal necrosis followed by

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relevant shrinkage of the ablated lesion [5] .

Human cells will generally undergo coagulative necrosis at temperatures above 50 °C. As the temperature increases, the time required for cells to denature decreases. Permanent damage to the cell membrane occurs if the temperature is above 60 °C and is followed by charring and drying of the tissue. During radiofrequency ablation (RFA), an alternating current of approximately 480 KHz is passed through the tumor using a needle electrode. This generates ionic agitation that results in frictional heat production causing cell death [6]. RFA can be used to treat benign thyroid nodules and inoperable recurrent thyroid cancer located in the surgical bed and lymph nodes. RFA is indicated in benign thyroid nodules for clinical problems associated with the nodule, such as symptoms (e.g., neck pain, dysphasia, foreign body sensation, discomfort, and cough), cosmetic problems, or thyrotoxicosis in autonomous functioning thyroid nodule (AFTN) cases [7]. In contrast, radiofrequency ablation is rarely used for the treatment of thyroid cysts or nodules, which are generally fluid [8]. In addition, surgery is conventionally recommended for the removal of excess abnormal growth tissue [9, 10]. However, the question remains as to which approach is more effective for treating benign thyroid nodules. Therefore, this systematic review and meta-analysis investigated the two approaches to determine which showed the lowest recurrence rate.

Materials and Methods

This review was conducted and performed in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines [11] and registered in the Prospective Register of Systematic Reviews (PROSPERO) with the unique number CRD42024506431. A comprehensive search strategy was implemented to identify relevant studies, which were then screened and selected based on the criteria outlined in the PRISMA guidelines.

Study design

The following focused research question was proposed using the Participants (P), Intervention (I), Comparison (C), and Outcome (O) format: “What is the recurrence rate of benign thyroid nodules after radioactive iodine ablation or lobectomy?”

The PICO criteria for this review were as follows:

P (Participants) – patients with benign thyroid nodules

I (Intervention) – patients with radioactive iodine ablation

C (Comparison) – patients with lobectomy

O (Outcome) – effect of radioactive iodine ablation or lobectomy on recurrence rate

Database search

The literature search used the electronic databases PubMed, Science Direct, and Europe PMC with the designated PICO keywords “radiofrequency ablation”, “lobectomy”, “benign thyroid nodule”, and “recurrences”. A thorough assessment of the titles and abstracts of each study was conducted to determine if they met the criteria for full-text analysis. The obtained studies were then screened further based on the eligibility criteria. The inclusion criteria were as follows: published within the last 50 years (1973–2022) and involved a randomized clinical trial or observational study (cohort, case-control, or cross-sectional) and the analysis of a minimum of one intervention approach (radiofrequency ablation or lobectomy) in benign thyroid nodule patients with appropriate recurrence data. The criteria for exclusion were as follows: in vitro studies that did not involve humans as study samples; case reports, case series (cases < 10), or reviews; and main manuscript in a language other than English or Indonesian.

Study selection

Two assessors (EBB and FNH) selected the studies independently. Discrepancies between the two appraisers were resolved through discussion, and if necessary, a third appraiser (PRI) was included in the selection process. The final selection was made based on the agreement of all authors.

For the first stage of screening, study selection is carried out based on title and abstract. For the second stage of screening, the results of the first stage of screening are selected based on the full text of the article and finally the study entered is in accordance with the inclusion criteria. Studies that cannot be obtained in full text or incomplete studies will be excluded from the selection stage. The selection process is carried out on the basis of a prism diagram.

Data extraction

Article selection was reviewed independently by three investigators with unanimous resolutions required for disagreements or conflicts that emerged. Data collected from the studies included author(s), publication year, study location, therapy method, tumor characteristics, and recurrence rate. Duplicate information from the databases was eliminated and only one of the records was included in the selected articles. When more than one article published the same data, the most recent study data was used.

Quality assessment

The study quality was established using a risk bias assessment. Cochrane’s risk of bias (ROB) tools were used for randomized clinical trials (RCT), whereas observational studies were measured using the quality appraisal of case series studies checklist (QACSS; Institute of Health Economics, Edmonton, Canada) [12, 13].

Data analysis

The recurrence rates for lobectomies and radiofrequency ablations within the eligible studies were assessed using the risk bias criteria of the Quality Appraisal of Case Series Studies Checklist and processed with RStudio version 2023.09.0+463 [14]. Heterogeneity of the results was identified and the findings were presented in Funnel and Forest plots.

Results

Based on the eligible criteria, 18 studies were included in this systematic review. The PRISMA study selection flow chart is shown in Figure 1. The studies included 4109 benign thyroid nodule patients who underwent radiofrequency ablation and 628 who received lobectomies. Follow-ups ranged from 1 month to 12 years. Further details are listed in Table 1.

The QACSS risk bias assessment returned the following results: Bernardi et al. [15] had >70 %; Che et al. [9], Kim et al. [16], Lin et al. [17], Lin et al. [18], Marchesi et al. [19], Radzina et al. [20], and Bom et al. [21] (seven studies) had percentages of 61–70 %; Guang et al. [22], Ji Hong et al. [23], Lim et al. [24], and Yan et al. [25] (four studies) returned 51–60 %, and the remaining 6 studies (Divarci et al. [26]; Hamidi et al. [27]; Lytrivi et al. [28]; Monpeyssen et al. [29]; Perez- Ruiz et al. [30]; and Rabuffi et al. [31]) showed less than 50 %. The entire QACSS results are listed in Table 2.

Furthermore, the overall bias risk was interpreted using a funnel plot and a forest plot for each recurrence rate after lobectomy and radiofrequency ablation (RFA) in benign thyroid nodule patients. The details are shown in Figures 2 and 3.

Among the 14 studies conducted utilizing radiofrequency ablation to treat benign thyroid nodules, 1409 cases were identified, of which 264 recurrences occurred during 1 to 8 years of follow-up. Within those studies, the recurrence rate proportion was 4 % (95 % CI, 2–10%). The heterogeneity value of benign thyroid nodule patients who underwent radiofrequency ablation was $I^2 = 92$ % and $\tau^2 = 2.3240$ at $p < 0.01$. This high heterogeneity value was not a result of the range of publication years or bias risk, since the p-values of those aspects were 0.5398 and 0.067, respectively (Figure 4).

Among the five studies conducted utilizing lobectomies to treat benign thyroid nodules, 628 cases were retrieved, of which 81 showed recurrences within 1 to 23 years of follow-up. Within those studies, the recurrence rate proportion was 11 % (95 % CI, 2–40 %). The heterogeneity value of benign thyroid nodule patients who underwent lobectomies was $I^2 = 92$ % and $\tau^2 = 3.261$ at $p < 0.01$. Similar to the radiofrequency ablation results, the high heterogeneity value was not caused by diverse publication years or bias risk (p-values 0.2814 and 0.3198, respectively) (Figure 5).

Discussion

Among the various methods of managing thyroid nodules, both minimally invasive and surgical approaches are available and each method has diverse varieties and specific complications. Of the two approaches, RFA generally produces fewer adverse effects and complications that emerge are often manageable over time. In contrast, lobectomies require time, competent surgery teams, and specific equipment. In addition, this method depends highly on the macroscopic visual field, which relates to a higher recurrence rate than that observed with the RFA method. Furthermore, open surgeries without minimal restrictions can create surgical scars that could create esthetic issues for the patient [9].

After comparing the recurrence rate of the two methods, no definite conclusion could be obtained, which is similar to the results of Che et al. [9]. This hindrance was caused by the lack of available studies, especially since all of the lobectomy intervention studies that were eligible included recurrence rates.

Although both interventions from this systematic

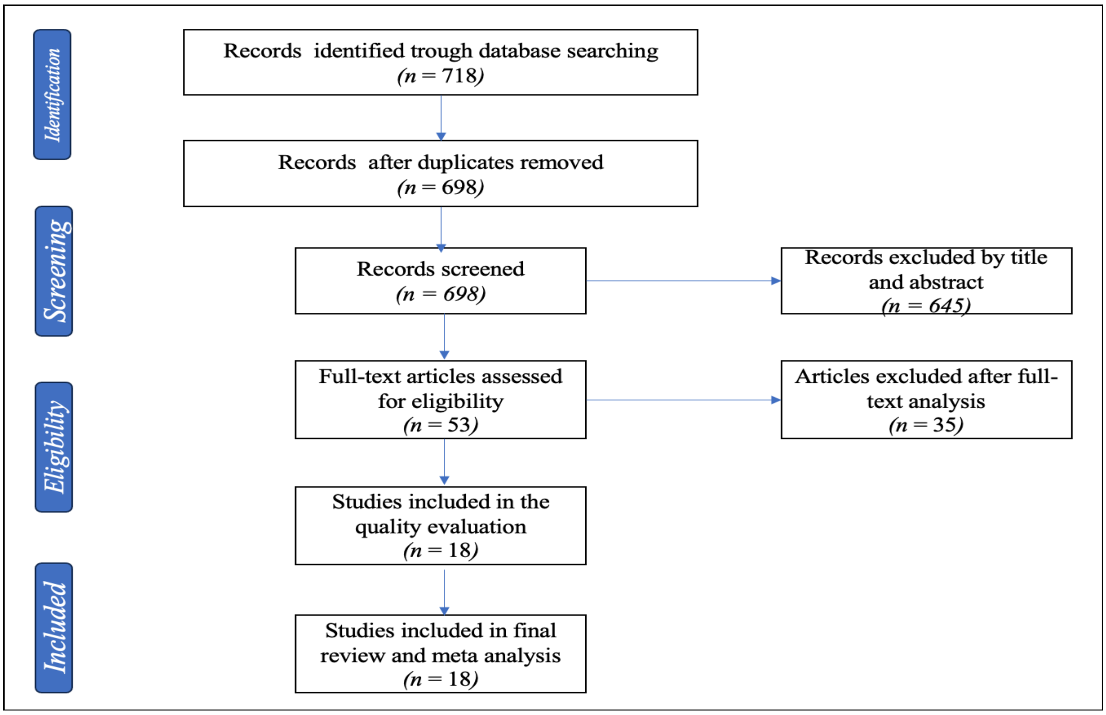

Figure 1. PRISMA Article Selection Process

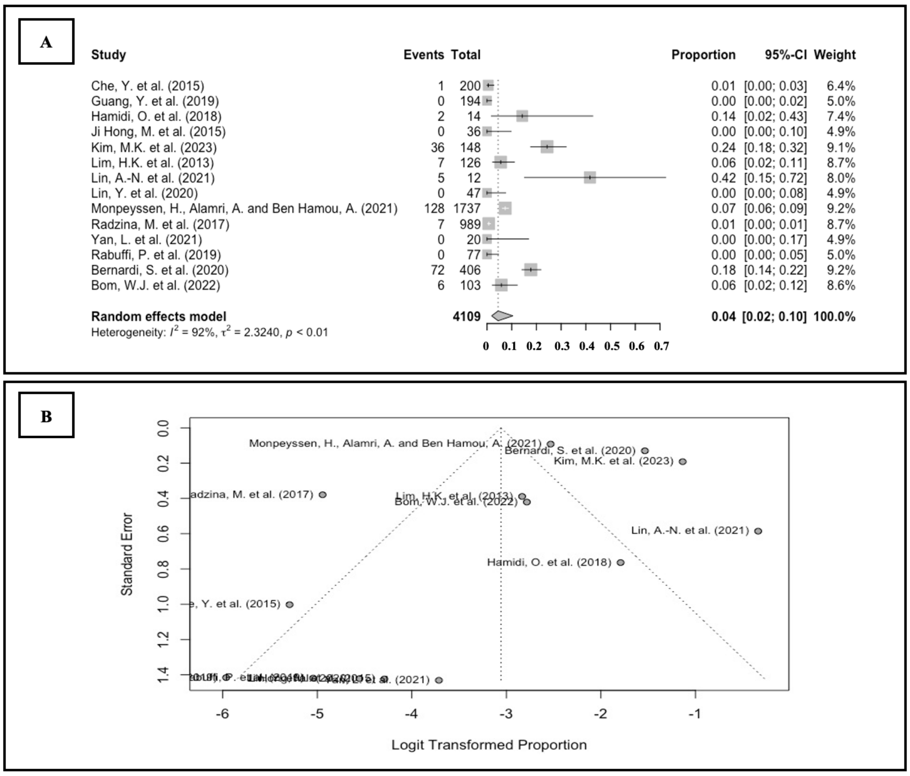

Figure 2. (a) Forest plot and (b) funnel plot of RFA of benign thyroid nodule patients

review showed statistically significant recurrence rate differences ($p<0.05$), the high heterogeneity value of the study population was an impediment and further investigations are required. The high heterogeneity value was determined not to relate to diverse publication years or bias risks, as assessed by the QACSS criteria.

The limitations of this study included the absence of data directly comparing both interventions under the same treatment and similar population characteristics, the homogeneity of the studies utilized, and the small number of study samples discovered for this systematic review and meta-analysis. Based on this systematic review of 18 studies, the recurrence rate of patients with lobectomy interventions was statistically significantly higher than that

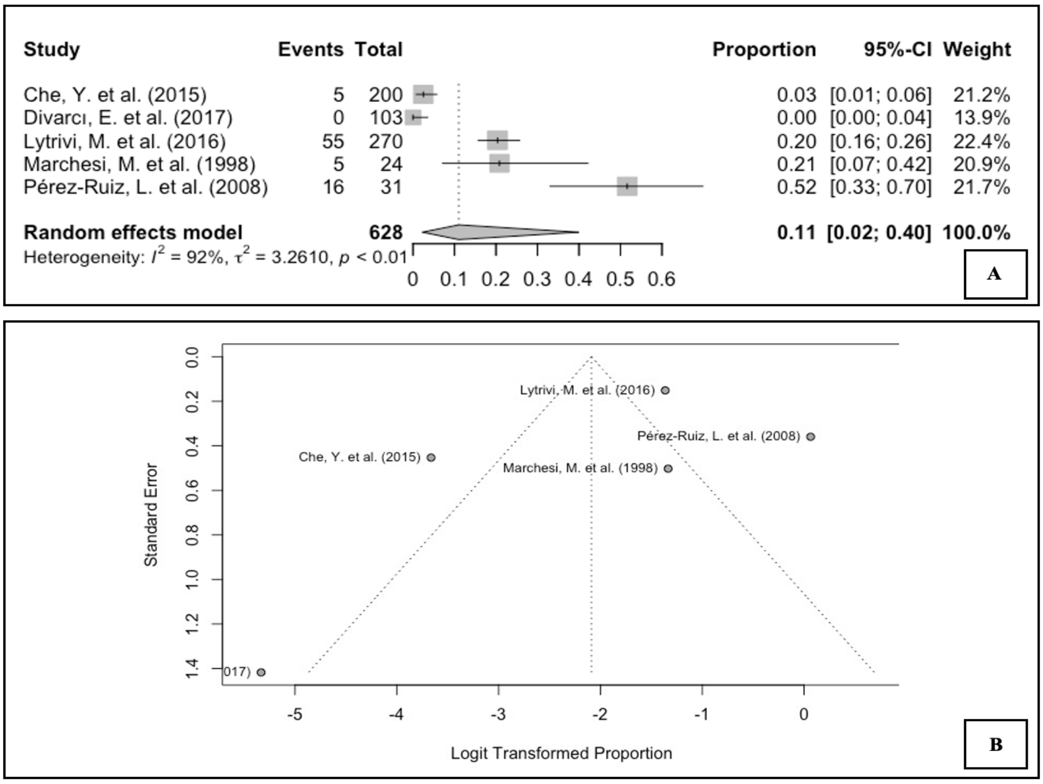

Figure 3. (a) Forest plot and (b) Funnel plot of lobectomy at benign thyroid nodule patients

Table 1. Study Characteristics

No	Author and publication year	Country of study	Treatment type	Total cases	Type of tumor /histological pattern	Follow-up time	Recurrence
1	Che et al. (2015) [9]	United States	Surgery (thyroidectomy and lobectomy): 200 RFA : 200	400	Nodular goiter	1 year	Surgery: 5 cases RFA: 1 case
2	Divarcı et al. (2017) [26]	Turkey	Nodulectomy / Lobectomy Total thyroidectomy	103	Thyroid nodule with low risk of differentiated thyroid carcinoma Thyroid nodule with high risk of differentiated thyroid carcinoma	2–10 years	No recurrence
3	Guang et al. (2019) [22]	China	RFA	194	Benign solid thyroid nodule	1,3,6,12,18,24 month	No recurrence
4	Hamidi et al. (2018) [27]	United States (Minnesota)	RFA: 38	14	Nodule echogenicity solid mixed	0,3,6,12,24	5.65–24.1 %
5	Ji Hong et al. (2015) [23]	Republic of Korea	RFA	36	Benign thyroid nodules	1–12 months	No recurrence
6	Kim et al. (2023) [16]	Republic of Korea (Seoul)	RFA	148	Benign thyroid nodules	6–12 months	35 cases
7	Lim et al. (2013) [24]	Germany	RFA	126	Solid thyroid nodule	4 years	7 cases
8	Lin et al. (2021) [17]	Taiwan	RFA	12	Benign non-functioning thyroid nodule	1,6,12 months	5 cases
9	Lin et al. (2020) [18]	France	RFA	47	Partially cystic thyroid nodules	1,3,6,12 months	No recurrence
10	Lytrivi et al. (2016) [28]	England	Thyroid lobectomy (hemithyroidectomy with isthmectomy)	270	Benign unilateral thyroid nodule	12–277 months	55 cases
11	Marchesi et al. (1998) [19]	Italy	Lobectomy	24	Follicular adenoma: 6 Nodular hyperplasia: 18	4 years	5 cases
12	Monpeyssen et al. (2021) [29]	Switzerland	RFA	1737	Solid thyroid nodule	1–70 months	128 cases
13	Pérez-Ruiz et al. (2008) [30]	England	thyroid isthmectomy	31	Solid Mix cystic with solid	15 months–12 years	16 cases
14	Radzina et al. (2017) [20]	Italy	RFA	989	Benign thyroid nodule	1–92 months	7 cases
15	Yan et al. (2021) [25]	England	RFA	20	Benign thyroid nodule	3,6,12,24 months	No recurrence
16	Rabuffi et al. (2019) [31]	Italy	RFA	77	Solid thyroid nodule Completely solid with fluid	6–12 months	No recurrence
17	Bernardi et al. (2020) [15]	United States	RFA: 216 LA: 190	406	Solid nodule Predominantly solid nodule Predominantly cystic nodule	1,2,3,4,5 years	155 cases total 43 RFA 72 LA
18	Bom WJ et al. (2022) [21]	Netherlands	RFA	103	Solid thyroid nodule: 85 Predominantly solid: 18	6–12 months	6 cases

Table 2. QACSS Risk bias Assessment

Study/ Criteria	Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one center?	Were patients recruited consecutively?	Were the characteristics of the patients included in the study described?	Were the eligibility criteria (i.e., inclusion and exclusion criteria) for entry into the study clearly stated?	Did the patients enter the study at a similar point in their disease?	Was the intervention of interest clearly described?	Was follow-up long enough for important events and outcomes to occur?	Were losses at follow-up reported	Were adverse events reported?	Was the conclusion of the study supported by the results?	Were both competing interests and sources of support for the study reported?
Che et al. (2015) [9]	yes	no	unclear	yes	yes	unclear	yes	yes	yes	yes	yes	no
Divarcı et al. (2017) [26]	yes	no	unclear	yes	yes	unclear	yes	yes	no	no	yes	no
Guang et al. (2019) [22]	yes	yes	unclear	yes	yes	unclear	yes	yes	no	no	yes	no
Hamidi et al. (2018) [27]	yes	no	unclear	yes	no	unclear	yes	yes	no	yes	yes	no
Ji Hong et al. (2015) [23]	yes	no	unclear	yes	yes	unclear	yes	yes	no	no	yes	yes
Kim et al. (2023) [16]	yes	no	unclear	yes	yes	unclear	yes	yes	yes	yes	yes	no
Lim et al. (2013) [24]	yes	no	unclear	yes	yes	unclear	yes	yes	no	yes	yes	no
Lin et al. (2021) [17]	yes	yes	unclear	yes	yes	unclear	yes	yes	no	yes	yes	no
Lin et al. (2020) [18]	yes	no	unclear	yes	yes	unclear	yes	yes	no	yes	yes	yes
Lytrivi et al. (2016) [28]	yes	no	unclear	yes	yes	unclear	yes	yes	no	no	yes	no
Marchesi et al.(1998) [19]	yes	yes	unclear	yes	yes	unclear	yes	yes	no	yes	yes	no
Monpeyssen, Alamri and Ben Hamou (2021) [29]	yes	yes	unclear	no	yes	unclear	yes	yes	no	no	yes	no
Pérez-Ruiz et al. (2008) [30]	yes	no	unclear	yes	no	unclear	yes	no	no	no	yes	no
Radzina et al (2017) [20].	yes	yes	unclear	yes	yes	unclear	yes	yes	no	yes	yes	yes
Yan et al. (2021) [25]	yes	no	unclear	yes	yes	unclear	yes	no	yes	yes	yes	no
Rabuffi et al. (2019) [31]	yes	no	unclear	no	yes	unclear	yes	yes	no	yes	yes	no
Bernardi et al. (2020) [15]	yes	yes	unclear	yes	yes	unclear	yes	yes	no	yes	yes	yes
Bom WJ et al. (2022) [21]	yes	yes	unclear	yes	yes	unclear	yes	yes	no	yes	yes	no

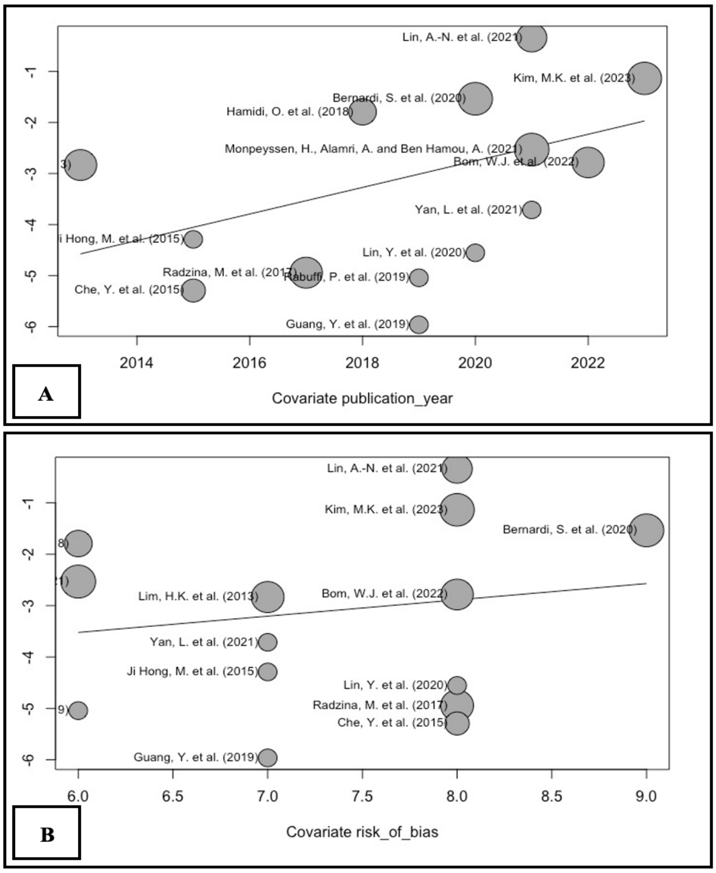

Figure 4. Meta Regression of Potential Heterogeneity Risks by (a) publication year and (b) bias risk of RFA in benign thyroid nodule patients

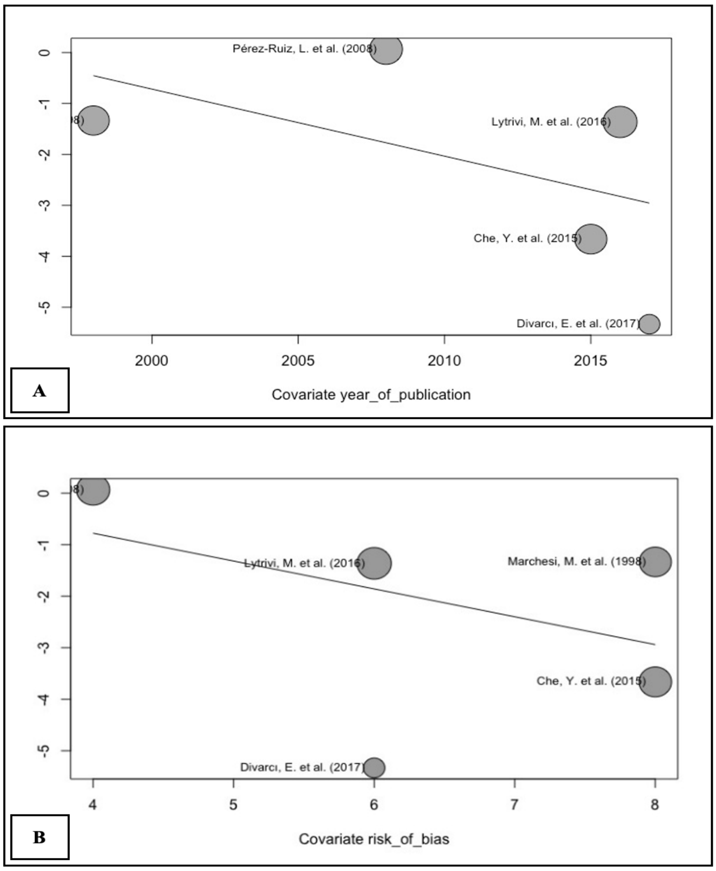

Figure 5. Meta Regression of Potential Heterogeneity Risks by (a) publication year and (b) bias risk of lobectomy in benign thyroid nodule patients

of patients who underwent RFA. However, this conclusion is not definitive due to the lack of direct comparisons between the two interventions in a single study, the absence of large study samples, and the homogeneity of the utilized studies.

Author Contribution Statement

EBB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. PRI: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Software, Validation, Visualization, Writing – original draft. FNH: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing.

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Data availability statement

All data relevant to the paper is included in the main text.

Study registration

This meta-analysis has been registered with the PROSPERO database and the unique identifying number is: CRD42024506431 on February 5, 2024. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024506431

Ethics approval

This research did not involve human subjects or any animal model; therefore, it was exempt from ethical clearance.

Conflict of interests

The authors declare no conflict of interest.

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